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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/901,612	07/28/97	FRANK B	HYZ-041FWC

18N2/1222

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EXAMINER	
LARSON, T	
ART UNIT	**PAPER NUMBER**
1809	

DATE MAILED: 12/22/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/901,612	Frank et al.
Examiner	**Group Art Unit**
Thomas G. Larson, Ph.D.	1809

☐ Responsive to communication(s) filed on _____.

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1, 8-20, 36, 40-50, and 207-225* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1, 8-20, 36, 40-50, and 207-225* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This application is a file wrapper continuation of Serial No. 08/467,397.

2. The disclosure is objected to because of the following informalities:

The specification at p. 29, ln. 2, indicates that oligonucleotide HBV6 has the sequence set forth in SEQ. ID. NO: 32, but Table 1, p. 16, shows that HBV6 has the sequence set forth in SEQ. ID. NO: 45. Note that Table 2 teaches that it is HBV-19 that has the sequence set forth in SEQ. ID. NO: 32.

Appropriate correction is required.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1, 8-20, 36, 40-50, and 207-225 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ 2d 1400, 1404; also see *Ex parte Forman,* 230 USPQ 546), the issue of enablement in molecular biology was considered and the factors to be considered in a determination of "undue" experimentation were summarized. These factors include (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of skill of those in the art; (e) the predictability of the art; (f) the amount of direction or guidance presented; (g) the presence or absence of working examples; (h) the quantity of experimentation necessary. See MPEP § 2164.01(a).

Regarding the breadth of the claims, claim 1 is broadly drawn to an oligonucleotide of unspecified length and sequence that is complementary to a portion of the HBV RNA *secondary* structure in the epsilon region of the HBV genome, and which inhibits HBV replication by an unspecified mechanism under unspecified conditions. Claims 8-20, 36 and 225 limit the oligonucleotide of claim 1 to *having* the sequence set forth in SEQ. ID. NOS: 7-19 and 45, wherein it is not apparent from the specification if the transitional language "having" is intended to be open or closed (see MPEP § 2111.03). Claims 40-47 and 207-223 limit the oligonucleotide of claims 1, 17, or 19 to having various chemical modifications, and claims 47, 48 and 224 are drawn to kits comprising the oligonucleotides of claim 1 or 19. Claim 50 is broadly drawn to a pharmaceutical composition comprising at least one oligonucleotide of claim 1.

Concerning the nature of the invention, the invention is complex requiring the artisan to determine effective target sequences using assays based on physiological systems which are unpredictable in nature (see below). The invention of claim 50, in specific, requires the artisan to

overcome a large number of obstacles to the successful practice of oligonucleotides in a therapeutic capacity that are well-known in the art (see below).

With regard to the prior art, determining effective target sequences for oligonucleotides is well known in the art to be unpredictable, even when given a target mRNA sequence, is unpredictable. Gewirtz et al. teach that intracellular events such as the formation of secondary structure by targeted nucleic acids and intracellular protein binding render target sequences inaccessible and impact upon the inhibitory activity of antisense molecules (p. 3161, col. 2, 2nd full ¶-¶ bridging pp. 3161-3162). Note that the instant claims are specifically drawn an oligonucleotide targeted to a region of secondary structure where the target site is sequestered by the RNA structure as depicted in Figure 3 of the disclosure. Gewirtz et al. characterize the selection of effective target sequences as a "hit or miss process" (p. 3161, ¶ bridging cols. 2 & 3, lns. 12-16) and teach that determining the accessibility of an mRNA target sequence is "...a significant impediment to the application of this technique in many cell systems (p. 3161, sentence bridging cols. 2 & 3). Zon et al. teach that the selection of effective target sequences is unpredictable with "no established selection rules" and "no reliable guidelines" for the identification of such sequences (p. 91, 1st full ¶). Hoke et al. (US Patent 5,585,479) teach that effective target sequences must be determined experimentally (col. 14, ln. 65-col. 17, ln. 7) and that "there are no rational explanations or rules that would predict active (antisense target) sequences"(col. 16, lns. 50-53). With respect to the pharmaceutical composition of claim 50, the successful application of oligonucleotides as anti-viral pharmaceutical compositions is unknown in

the field. Gura ("A1" on PTO-1449 filed 2/3/97) teaches several art-recognized obstacles to the successful therapeutic application of oligonucleotides, that include difficulties getting the oligonucleotides to the targeted tissues (Gura, p. 575, col. 1, 2nd ¶). Gewirtz et al. teach that a "major problem in this field is the ability to deliver ODN (oligodeoxynucleotides) into cells and have them reach their targets" (p. 3161, col. 3, lns. (6-10). Rojanasakul teaches that the effective use of oligonucleotide therapeutics "has been limited due to several problems.... (B)ecause of their large size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting and affinity...to the target site pose major challenges to the successful utilization of these compounds" (abstract, lns. 8-13). Whitton teaches that the successful treatment of viral infections using nucleic acids is unknown in the art (p. 267, ¶ 1; pp. 271-272, section E; pp. 292-294, section IV).

Concerning the predictability of the art, the determination of effective antisense sequences is inherently unpredictable, as admitted by applicant at pp. 8-9, bridging ¶, of the response filed 9/25/96, and as evidenced by the teachings of Gewirtz et al, Hoke, and Zon et al. above. Gewirtz et al. further state that the results obtained from experiments involving the application of oligonucleotides to inhibit physiological activities have frequently produce results that were "highly variable", "non-informative", "misleading", or "unreproducible" (p. 3161, col. 2, 1st full ¶). Gura teaches that there are uncertainties regarding the mode of action of antisense oligonucleotides (Gura, p. 575, col. 1, 2nd ¶).

With respect to the amount of guidance provided in the disclosure, the disclosure provides general teachings concerning antisense oligonucleotides as well as listing of oligonucleotides with potential anti-HBV activity (Tables I and II). However, the specification lacks the specific teachings that would enable the artisan to overcome the obstacles to the determination of effective antisense target sequences taught by Gewirtz et al, Hoke, and Zon et al, as discussed above. The specification also lacks the specific disclosures that would allow the artisan to overcome the obstacles to practicing the invention as a pharmaceutical composition taught by Gewirtz et al, Gura, Rojanasakul, and Whitton, as discussed above.

Concerning working examples, no working example appears to be disclosed for the inhibition of HBV replication by oligonucleotides with sequences consisting of or comprising those of SEQ. ID. NOS: 7-19, and 45 alone. A single working example is provided for the use of oligonucleotides of SEQ. ID. NOS: 6 and 18 together (p. 23, lns. 25-32). Although this example appears to enable a composition comprising two oligonucleotides consisting of SEQ. ID. NOS: 6 and 18, it is not clear that it is sufficient to enable each of these oligonucleotides individually. An example is provided for the application of SEQ. ID. NO: 18 in a kinetic PCR assay(p. 29, lns. 7-35), but it is not clear from the specification how the results of this assay relate to antiviral activity of oligonucleotides, especially in view of the result that an oligonucleotide of random sequence appears to show appreciable activity in the assay (Table 3, p. 29). Working examples are provided for the targeting of the epsilon region of the HBV transcript using various oligonucleotides, but these examples do not appear to exemplify the claimed embodiments and it

is not clear that a correlation can be drawn between these examples and the claimed oligonucleotides. Given the unpredictability of determining effective antisense sequences, the skilled artisan would appear to have no basis for judging effective antisense sequences that meet the limitations of the claims based on these examples. See MPEP § 2164.02.

Regarding the amount of experimentation, due to the absence of the required teachings in the prior art and in the specification regarding the determination of effective antisense target sequences, and due to the lack of the appropriate working examples in the specification, the skilled artisan would be required to engage in experimentation to practice the claimed invention. Given the unpredictability of the art, the complexity of the invention, and the breadth of the claims, such experimentation would be extensive and of a "hit or miss" nature.

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation. See MPEP § 2164.01(a), last ¶. Since the skilled artisan could not have practiced the claimed invention without engaging in undue experimentation, the specification fails to provide an enabling disclosure.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 8-16, 18, 20, 36 and 207-210 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-16, 18, 20, 36, and those dependent thereon are indefinite for using the transitional language "having" because it is not clear whether "having" denotes open or closed transitional language and it can not be determined from the specification whether open or closed language is intended. See MPEP § 2111.03. It is suggested that well-defined transitional language, such as "consisting of" or "comprising" be used.

7. No claim is allowed.

8. Certain papers related to this application may be submitted to Art Unit 1809 by facsimile transmission. The FAX numbers are (703) 308-4242 and (703) 308-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Unofficial papers, such as draft responses, may be transmitted to the examiner directly at (703) 308-0294. It is recommended that the examiner be notified when a fax is sent to this number.

9. Any inquiry concerning this communication or earlier communications should be directed to Dr. Thomas Larson, whose telephone number is (703) 308-7309. The examiner normally can be reached Monday through Friday from 9:00 AM to 5:30 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

Thomas G. Larson, Ph.D.
Examiner

Thomas G. Larson, Ph.D.
Patent Examiner
Group 1800